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Prospective study of alcohol consumption and the risk of colorectal cancer before and after folic acid fortification in the United States

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Abstract

Purpose—To evaluate the influence of alcohol consumption on the risk of colorectal cancer according to folic acid fortification period in the United States.

Methods—We evaluated the association between alcohol consumption and colorectal cancer by fortification period (before 1998 vs. after 1998) in two prospective cohort studies, Nurses' Health Study (NHS) of women and Health Professionals Follow-up Study (HPFS) of men, in which 2,793 invasive colorectal cancer cases were documented.

Results—Alcohol consumption was associated with an increased risk of colorectal cancer. Among non-users of multivitamins and/or folic acid supplements, the pooled multivariate relative risk (RR) for ≥30g/d drinkers versus non-drinkers was 1.36 (95% CI, 1.09–1.70; *p* for trend, 0.02). The effect of alcohol consumption was slightly stronger in the pre-folic acid fortification period (1980 NHS/1986 HPFS-1998) than in the post-fortification period (1998–2008); the pooled multivariate RRs for ≥30g/d drinkers versus non-drinkers were 1.31 (95% CI, 1.00–1.71; *p* for trend, 0.10) in the pre-fortification period and 1.07 (95% CI, 0.69–1.65; *p* for trend, 0.67) in the post-fortification period.

Conclusions—Folic acid fortification may attenuate the adverse effect of high alcohol consumption on the risk of colorectal cancer.

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INTRODUCTION

Colorectal cancer is a major burden of disease worldwide. Based on International Agency for Research on Cancer, colorectal cancer was the 4th in cancer incidence and the 5th cause of cancer death worldwide in 2008 (1). High alcohol intake is an established risk factor for colorectal cancer (2–6). An expert review panel concluded alcohol consumption as a "convincing" risk factor for colorectal cancer in men and "probable" risk factor in women (7). However, the mechanism by which alcohol causes colorectal carcinogenesis remains unclear.

Folate deficiency amplifies the positive association between alcohol and colorectal cancer (8–12). As a folate antagonist, alcohol inhibits folate-mediated methionine synthesis, causing abnormal DNA methylation which is frequently observed in colorectal neoplasia (13–17). The combination of high alcohol and low folate intake has been associated with much higher risk of colorectal cancer compared to intake of high alcohol or low folate individually, while high folate intake mitigates the adverse influence of high alcohol consumption on colorectal cancer (18–22).

Thus, an increase in folate intake by folic acid fortification in grain-based foods in the United States might reduce the adverse effect of alcohol on colorectal carcinogenesis, especially in populations not taking additional folate supplementation. We examined whether folic acid fortification attenuates the influence of alcohol consumption on colorectal cancer in two prospective cohort studies, the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS).

SUBJECTS AND METHODS

Study Population

The NHS enrolled 121,700 female registered nurses aged 30–55 years in 1976 (23). The HPFS included 51,529 male health professionals aged 40–75 years in 1986. In both cohorts, we have subsequently updated information biennially with greater than 90% follow-up. In this study, we only included participants with alcohol intake information at baseline of 1980 in the NHS and 1986 in the HPFS with plausible energy intakes (600–3500 kcal/d for women and 800–4,200 kcal/d for men) and no diagnosis of cancer (except non-melanoma skin cancers) or ulcerative colitis.

In both cohorts, we requested permission to obtain medical records and pathology reports from participants who reported colorectal cancer on our biennial questionnaires. We identified fatal cases from the National Death Index and from next-of-kin. Study physicians blinded to exposure data reviewed all medical records to confirm cases of colorectal cancer. We based our analysis on all incident colorectal cancers, and excluded the small number of non-adenocarcinoma cases and carcinomas *in situ*.

The procedures and protocols of the study were approved by the Institutional Review Boards at Brigham and Women' Hospital.

Dietary and Nondietary Data

A semiquantitative food-frequency questionnaire (FFQ) with approximately 60 food items was sent to NHS participants in 1980. An expanded FFQ with approximately 130 food items were administered to women in 1984, 1986, and every 4 years thereafter. Similar expanded version of FFQ was administered to men in HPFS in 1986 and every 4 years thereafter. Participants were asked how often, on average, they had consumed each type of food or beverage including alcohol during the past year. Responses on frequencies of a specified

serving size for each food item were converted to average daily intakes. Quantities of nutrients including folate from foods were calculated by multiplying the reported frequency of each food by the nutrient content of one serving of that food primarily on the basis of the US Department of Agriculture Nutrient Database (24). Caloric intake was adjusted for by using the nutrient residual method (25). As the United States Food and Drug Administration (FDA) mandated fortification of enriched grain-based foods with folic acid beginning in 1998, we took into account the fortification of folic acid for the assessment of folate intake. Information on use of multivitamins and folic acid supplements was asked from 1980 (NHS) and from 1982 (HPFS), respectively, and onwards every two years.

We determined alcohol intake by multiplying the frequency of specific alcoholic beverage by its ethanol content; 12.8 g of alcohol for a 12-oz can or bottle of beer, 11.3 g for a 12-oz can or bottle of light beer, 11.0 g for a 4-oz glass of wine, and 14.0 g for a standard drink of liquor.

Drinking pattern was assessed in 1988 in NHS and HPFS. Participants were asked the usual number of days of alcohol consumption in a typical week and the largest number of alcohol drinks consumed in one day in a typical month (none, 1–2 , 3–5, 6–9, 10–14, or 15+ drinks).

To evaluate the validity of the reported alcohol consumption measured by the FFQ, comprehensive diet records and plasma high-density lipoprotein (HDL) levels were obtained from a subset of participants in the cohorts (26). Mean daily intakes of alcohol, as assessed by the FFQ and by the diet records were very similar; the Spearman correlation coefficient was 0.90 in women and 0.86 in men. In addition, based on the information of alcohol intake reported by FFQ, the difference in plasma HDL level between male abstainers vs. drinkers of over 39 g/d was 11.8 mg/dl, which is a similar magnitude determined from short term intervention studies of alcohol (26).

Statistical analyses

We conducted cohort-specific analyses for the association between alcohol intake and colorectal cancer risk among whole population as well as individuals confined to prefolic acid fortification period (1980 NHS/1986 HPFS-1998) and post-fortification period (1998–2008). We also conducted a secondary analysis excluding users of multivitamins and/or folic acid supplements.

In each analysis, alcohol consumption was divided into categories using identical cutpoints across the studies. To reduce within-person variation and to better estimate long-term intake, we used the cumulative average intake of alcohol as reported on all available questionnaires up to the start of each 2-year follow-up interval (27). Participants contributed person-time from the date of return of their baseline questionnaire until the date of diagnosis of colorectal cancer, death, or end of follow-up (June 2008 for NHS and January 2008 for HPFS), whichever came first for the overall analysis.

We calculated relative risks (RRs) for each study by dividing the incidence rate in one category by the incidence rate in the reference category (non-drinkers); we used Cox proportional hazards regression with SAS PROC PHREG (SAS V9.2; SAS Institute Inc, Cary, NC) to control for multiple covariates simultaneously and to calculate 95% confidence intervals (CIs). In the multivariate models, we adjusted for known or suspected colorectal cancer risk factors (as footnoted in Table 2). For these covariates, we used cumulative average dietary intakes; nondietary covariates were updated every 2 years except height. Because age-adjusted results were similar to multivariate results, we presented only multivariate results.

We combined cohort-specific $\log_e$ RRs using a random effects model to achieve maximum statistical power (28). A two-sample Wald test was used to assess the extent of heterogeneity across the pre- and post- folic acid fortification periods among individuals who consumed alcohol >30 g/d. To calculate the *P* value for the test for trend, participants were assigned the median value of their category of alcohol, and this variable was treated as a continuous term.

Among individuals in the post-fortification period, we further examined whether the associations between alcohol intake and colorectal cancer risk varied by subgroups defined by family history of colorectal cancer and intake of other nutrients involved in one-carbon metabolism including choline, betaine, vitamin B6, vitamin B12, and methionine. We conducted analyses stratified by family history (yes or no) and onecarbon nutrients (low or high), and assessed statistical significance of interaction by using the Wald test for cross-product terms of the one-carbon nutrients or family history and alcohol intake in the multivariate regressions. All statistical analyses were two-sided and carried out using SAS V9.1 (SAS Institute Inc). $P<0.05$ were considered significant.

RESULTS

During follow-up of 28 years among 87,856 women (2,291,198 person-years) and 22 years among 46,874 men (895,185 person-years), we documented 2,793 cases of invasive colorectal cancer (1,628 women and 1,165 men).

The baseline characteristics of participants according to folic acid fortification period are presented in Table 1. Compared with individuals in the pre-fortification period, individuals in the post-fortification period in both women and men were less likely to consume alcohol and to smoke. They were also more likely to have a higher BMI, higher intakes of calcium, folate, betaine, vitamin B6, and vitamin B12, and lower intakes of red meat, choline, and methionine. Women in the post-fortification period were more likely than those in the pre-fortification period to use postmenopausal hormones, to drink, and to have a family history of colorectal cancer.

We examined the association between alcohol consumption and colorectal cancer risk in the whole population as well as individuals in pre- or post- fortification period (Table 2). In the whole follow-up period, we found that alcohol consumption was associated with an increased risk of colorectal cancer. Compared with non-drinkers, the the pooled multivariate RR for >30g/d drinkers versus non-drinkers was 1.35 (95% CI, 1.14–1.59; *p* for trend, 0.004). The association did not materially change when the analysis was confined to pre-folic acid fortification period (1980[NHS]/1986[HPFS]-1998); the pooled multivariate RR for >30g/d drinkers versus non-drinkers was 1.32 (95% CI, 1.06–1.63; *p* for trend, 0.10). In contrast, alcohol consumption was not significantly associated with an increased risk of colorectal cancer in the post-fortification period although the test for heterogeneity by period was not statistically significant (*p*-value, 0.45); the pooled multivariate RRs for >30g/d drinkers versus non-drinkers was 1.13 (95% CI, 0.85–1.51; *p* for trend, 0.17).

We also examined drinking pattern in relation to colorectal cancer risk; either frequency of drinking or quantity of drinking was not associated with the risk of colorectal cancer (data not shown).

Because participants taking supplemental folic acid might have been less affected by folic acid fortification, we conducted a secondary analysis excluding users of multivitamins and/or folic acid supplements (Table 3). Overall, the effect of folic acid fortification on high alcohol intake and colorectal cancer was similar in this supplement non-user group than in the whole population group. Among supplement non-users, the pooled multivariate RRs for over 30g/d drinkers versus non-drinkers were 1.36 (95% CI, 1.09–1.70; *p* for trend, 0.02),

1.31 (95% CI, 1.00–1.71; *p* for trend, 0.10), and 1.07 (95% CI, 0.69–1.65; *p* for trend, 0.67) for whole period, pre-fortification period, and postfortification period, respectively. We also examined the association between alcohol intake and colorectal cancer among those taking multivitamins or folic acid supplement. Along with our main findings, we found more pronounced increase in colorectal cancer for ≥30 g/d of alcohol intake versus non-drinkers in pre-fortification era (RR, 1.40; 95% CI, 1.03–1.91) than post-fortification era (RR, 1.15; 95% CI, 0.80–1.65).

The full effect of folic acid fortification may take several years. Therefore, we further divided post-fortification period into two periods (1998–2004 vs. 2004–2008) and evaluated the relationship between alcohol intake and colorectal cancer risk. The pooled multivariate RRs for over 30g/d drinkers versus non-drinkers were 1.06 (95% CI, 0.74–1.51; *p* for trend, 0.44) for 1998–2004 and 1.21 (95% CI, 0.68–2.17; *p* for trend, 0.43) for 2004–2008.

Even in the post-fortification period, there could be subpopulations which are susceptible to adverse effect of alcohol. To examine this, we evaluated the effect modification by family history (yes or no) and other one-carbon nutrients (low and high) on the association between alcohol intake and colorectal cancer risk among individuals in the post-fortification period (Supplementary Table 1). The association differed by the intake of methionine. Compared with non-drinkers, the pooled multivariate RRs were 0.96 (95% CI, 0.68–1.35) for alcohol consumption of ≥15g/d among those with high intake of methionine and 1.39 (95% CI, 1.06–1.83) for the same comparison among those with low intake of methionine (*p* for interaction =0.05). Intake of other one-carbon nutrients as well as family history did not modify the association between alcohol consumption and colorectal cancer risk (all *p* for interaction ≥0.40).

DISCUSSION

We found that the adverse effect of alcohol consumption on colorectal cancer appeared to increase with higher intake of alcohol, with the greatest increase in risk found among individuals who consumed over 30g/d of alcohol. When we divided the follow-up based on folic acid fortification period, similar positive association for alcohol consumption and colorectal cancer was found among individuals in the pre-folic acid fortification period. However, the effect of alcohol was attenuated and non-significant in the post-fortification period.

Consistent with our findings, most previous epidemiologic studies support the adverse role of alcohol intake on colorectal neoplasia with an increase in risk among individuals with >1 drink/d of alcohol (29). However, these studies were largely conducted in populations who were not fortified by folic acid or before fortification period.

Considerable evidence demonstrates that alcohol interferes with the role of folate in one-carbon metabolism, a complex network of interrelated biochemical reactions that involve the transfer of one-carbon (methyl) groups from one compound to another (13, 17, 30). As a central element in one-carbon metabolism pathway, folate donates a single carbon to homocysteine to form methionine which further transfers a methyl group to produce S-adenosylmethionine, thereby involved in DNA methylation reactions. On the other hand, folate-induced deoxythymidylate (dTMP) is required for DNA synthesis and repair (31). Abnormal DNA methylation and gene expression due to folate deficiency may contribute to carcinogenesis of numerous types of tissues including colorectum, possibly by influencing activation of tumor suppressor genes and/or oncogenes (14, 16, 32–34). Furthermore, several epidemiologic studies have found lower intakes of folate related to colorectal cancer risk (8–12).

Alcohol impairs the bioavailability of dietary folate as well as folate-dependent intermediary metabolisms. Such antagonistic impact of alcohol on folate metabolism may lead to an increase in folate requirements among high alcohol consumers. The increased need for folate in turn causes relative deficiency of folate and further an increase in risk of colorectal cancer (13, 17, 35). To address this hypothesis, some studies have evaluated the joint effect of high intake of alcohol and low intake of folate on colorectal neoplasms, and most of them found an elevated risk of colorectal cancer or adenoma among individuals, especially men, with high alcohol-low folate intake compared to those with low alcohol-high folate intake (13). Also, high alcohol consumption did not provide an excess risk of colorectal cancer if folate intake was high (19). It is therefore plausible that an increase in folate intake by folic acid fortification might reduce the magnitude of alcohol's adverse effect. It is also reasonable to assume that the impact of folic acid fortification would be most evident among those who did not get folic acid from other sources (e.g. multivitamins). In support of this hypothesis, our data showed an association between alcohol consumption and colorectal cancer prior to folic acid fortification but the association was attenuated and non-significant after fortification among those who did not get folic acid from other sources.

Folate-deficiency anemia, a decrease in red blood cells due to a lack of folate, is frequently found among high alcohol consumers (36). Our results suggest the possibility that folic acid fortification may benefit individuals with folate-deficiency anemia due to high alcohol consumption.

Even in the post-fortification period, alcohol may be harmful when intake of other onecarbon nutrients was limited, because alcohol may also act through affecting these nutrients related to methyl group availability, including betaine, methionine, vitamin B6, vitamin B12, and choline (15, 37, 38). Laboratory animal studies have shown that combined deficiency of these nutrients causes genomic DNA hypomethylation, and further influences colon carcinogenesis (39, 40). Epidemiological studies have also reported that inadequate intakes of these nutrients may have an impact on the risk of colorectal neoplasms (13, 41–46). However, studies considering the combined effect of alcohol, folate, and other nutrients are rare, although a synergistic effect of combination of folate and other nutrients such as methionine, vitamin B6, and vitamin B12 on colorectal cancer has been suggested (13, 43). In the HPFS, we have previously observed that high alcohol consumption prominently increases the risk of colon cancer (three fold risk) among men with low methionine and folate intakes compared with non-drinkers with high intake of these nutrients (19). Similarly, a prospective study of U.S. non-institutionalized population including African Americans and Whites found a significantly increased risk for men who consumed high alcohol-low folate-low methionine diets when compared to male non-drinkers who consumed high folate and high methionine diets (47). In support of these observations, we found a significant positive association between alcohol intake and risk of colorectal cancer among individuals with low intake of methionine, but not among those with high intake of methionine in the post-folic acid fortification period.

A history of colorectal cancer in a first-degree relative (e.g., parent or sibling) is a wellknown risk factor of colorectal cancer (48). Previous case-control studies in different populations as well as our cohort studies have examined the association between alcohol consumption and colorectal cancer risk according to family history of colorectal cancer, and found that alcohol consumption is more strongly associated with the risk of colorectal cancer among individuals with family history than among those with no history (49–52). In our study, the effect of alcohol consumption on the risk of colorectal cancer was not different by family history of colorectal cancer in the post-fortification period, probably due to a predominant beneficial effect of high folate intake on alcohol-colorectal cancer association.

However, we cannot rule out the possibility that the observed result is due to a relatively small number of cases with positive family history in the post-fortification period.

Our study has several strengths. First, because of the prospective nature of the study and high rates of long-term follow up, the recall bias and selection bias that might occur in case-control studies were unlikely to account for our findings. Second, repeated measurements of both dietary and non-dietary factors including alcohol consumption allowed us to divide the follow-up into pre- and post-fortification periods and to evaluate the association between alcohol and colorectal cancer in each period. Even within the periods, we used repeated and updated information on alcohol consumption, folate intake, and other covariates, and thus reduced misclassification of these factors.

We acknowledge limitations to our study. Residual confounding is a concern in observational studies. However, adjustment for multiple colorectal cancer risk factors only made minimal influence on our findings, suggesting little potential for residual or uncontrolled confounding. Also, alcohol consumption was self-reported in our study. However, because the participants of both women and men were all health professionals, the accuracy of self-reported alcohol consumption is likely to be high. In addition, the validity of the self-reported alcohol consumption measured by the FFQ has been verified (26). Also, because the effect of folic acid fortification on alcohol consumption and colorectal cancer may not appear immediately, longer follow-up after fortification period may be desirable to better observe the impact of folic acid fortification. Finally, the difference of association between alcohol consumption and colorectal cancer by fortification period might not be completely due to fortification because other factors including age of the population had changed, although we tried to adjust for other factors as much as possible.

In conclusion, our study suggests that folic acid fortification may attenuate the adverse effect of high alcohol consumption on colorectal cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline characteristic of participants according to folic acid fortification period in the NHS and HPFS*

	Pre-fortification (1980/1986–1998)		Post-fortification (1998–2008)	
Characteristic	**NHS (1980)**	**HPFS (1986)**	**NHS (1998)**	**HPFS (1998)**
No.	87,856	46,874	69,330	28,548
Age (years)	46.2 (7.2)	53.8 (9.7)	63.8 (7.1)	64.3 (9.0)
Height (inches)	64.5 (2.4)	70.1 (2.8)	Same as pre-fortification	
BMI (kg/m2)	24.3 (4.8)	25.5 (3.3)	26.7 (5.3)	26.1 (3.6)
Family history of colorectal cancer (%)**	8.0***	13.7	15.0	14.0
Former or current postmenopausal hormone use (%)	18.5	NA	31.7	NA
Alcohol intake (g/d)	6.4 (10.5)	11.3 (15.4)	5.0 (9.1)	10.9 (14.0)
Non-alcohol drinkers (%)	32.1	23.7	20.3	23.5
Smoking status (%)				
Past	27.6	43.4	44.9	48.0
Current	28.9	10.0	10.5	5.0
Red meat as main dish (servings/d)	0.4 (0.3)	0.3 (0.2)	0.1 (0.1)	0.2 (0.2)
Total calcium intake (mg/d)	732.5 (314.6)	897.1 (424.4)	1268 (597.6)	1023.7 (481.3)
One-carbon nutrient				
Total folate intake (mcg/d)	365.3 (275.0)	480.2 (276.2)	633.9 (271.7)	717.6 (327.5)
Dietary folate intake (mcg/d)	258.0 (105.6)	356.5 (118.0)	392.0 (113.4)	463.2 (137.6)
Supplemental folic acid intake (mcg/d)	156.1 (354.5)	180.3 (279.2)	353.3 (250.4)	384.8 (296.1)
Total choline intake (mg/d)	360.1 (79.3)	399.8 (93.8)	298.8 (66.4)	375.7 (85.4)
Total betaine intake (mg/d)	96.6 (51.0)	130.2 (59.7)	102.8 (43.7)	130.9 (53.2)
Total vitamin B6 intake (mg/d)	3.0 (9.0)	8.6 (24.9)	14.9 (35.6)	15.3 (35.9)
Total vitamin B12 intake (mcg/d)	8.9 (20.3)	12.6 (18.2)	21.2 (34.8)	24.4 (44.3)
Total methionine intake (g/d)	1.9 (0.5)	2.2 (0.5)	1.6 (0.3)	2.0 (0.5)

*Age-standardized values; mean (SD) or %; NHS, Nurses' Health Study (NHS); HPFS, Health Professionals Follow-up Study

**Family history of colorectal cancer was asked in 1982, 1988, 1992, and 1996.

***Assessed in 1982

Table 2

Multivariate relative risk (RR) and 95% confidence interval (CI) of cumulative alcohol intake and colorectal cancer according to folic acid fortification period

Alcohol (g/d)	0	0.1–4.9	5.0–9.9	10–14.9	15–29.9	30+	*P* for trend
All (1980/1986–2008)							
NHS (women)							
No. of cases	335	716	208	147	149	73	
Multivariate RR *	1.00	1.16 (1.01–1.32)	1.11 (0.92–1.32)	1.22 (1.00–1.48)	1.13 (0.93–1.38)	1.30 (1.00–1.69)	0.15
HPFS (men)							
No. of cases	200	285	167	150	186	177	
Multivariate RR *	1.00	0.95 (0.79–1.19)	0.95 (0.77–1.17)	1.08 (0.87–1.35)	1.06 (0.86–1.30)	1.38 (1.11–1.72)	<0.001
Pooled (women and men)							
No. of cases	535	1001	375	297	335	250	
Multivariate RR *	1.00	1.06 (0.87–1.28)	1.04 (0.91–1.20)	1.15 (0.99–1.34)	1.10 (0.95–1.27)	1.35 (1.14–1.59)	0.004
Pre-fortification era (1980/1986–1998)							
NHS (women)							
No. of cases	207	367	102	88	76	44	
Multivariate RR *	1.00	1.13 (0.95–1.34)	1.01 (0.79–1.28)	1.27 (0.99–1.65)	1.05 (0.80–1.37)	1.18 (0.84–1.65)	0.54
HPFS (men)							
No. of cases	129	136	92	77	89	110	
Multivariate RR *	1.00	0.82 (0.64–1.05)	0.96(0.73–1.26)	0.95 (0.70–1.27)	0.97 (0.73–1.28)	1.42 (1.08–1.88)	0.001
Pooled (women and men)							
No. of cases	336	503	194	165	165	154	
Multivariate RR *	1.00	0.98 (0.72–1.33)	0.98 (0.82–1.18)	1.11 (0.83–1.48)	1.01 (0.83–1.22)	1.32 (1.06–1.63) **	0.10
Post-fortification era (1998–2008)							
NHS (women)							
No. of cases	237	180	79	45	50	28	
Multivariate RR *	1.00	1.03 (0.84–1.25)	1.31 (1.01–1.70)	0.94 (0.68–1.30)	1.30 (0.95–1.79)	1.24 (0.83–1.87)	0.12
HPFS (men)							
No. of cases	75	91	49	54	71	40	

Alcohol (g/d)	0	0.1–4.9	5.0–9.9	10–14.9	15–29.9	30+	*P* for trend
Multivariate RR *	1.00	1.06 (0.77–1.45)	0.95 (0.66–1.38)	1.10 (0.76–1.58)	1.21 (0.86–1.71)	1.04 (0.69–1.55)	0.64
Pooled (women and men)							
No. of cases	312	271	128	99	121	68	
Multivariate RR *	1.00	1.04 (0.88–1.23)	1.15 (0.84–1.56)	1.01 (0.79–1.29)	1.26 (1.00–1.59)	1.13 (0.85–1.51) **	0.17

The combined number of cases in pre- and post- fortification periods is not the same as total number of cases, because the exclusion conditions for the cases were applied to each baseline of pre- and postfortification period. NHS, Nurses' Health Study (NHS); HPFS, Health Professionals Follow-up Study

* Multivariate RRs are adjusted for age, gender (combined data only), total pack-years of smoking (<10, 10-<30, 30-<50, 50-<70, 70+), physical activity (quintiles of metabolic equivalent tasks/wk), body mass index (BMI) (<23, 23-<25, 25-<30, 30-<35, and 35+ kg/m^2), height (continuous), family history of colorectal cancer in parents and siblings (yes, no), history of endoscopy (yes, no), aspirin use (never, past, current use of 1–2, ≥3 tablets/wk), postmenopausal hormone (PMH) use (only in women; premenopausal, never, past, and current), red meat intake (quintiles), calcium intake from foods (continuous), multivitamin use (yes, no), and total energy intake (continuous)

** *P* for heterogeneity by fortification period was 0.45.

Table 3

Pooled multivariate relative risk (RR) and 95% confidence interval (CI) of cumulative alcohol intake and colorectal cancer according to folic acid fortification period among non-users of multivitamins and folic acid supplements

Alcohol (g/d)	0	0.1–4.9	5.0–9.9	10–14.9	15–29.9	30+	*P* for trend
All (1980/1986–2008)							
No. of cases	314	549	198	171	170	140	
Multivariate RR *	1.00	1.12 (0.97–1.29)	1.04 (0.86–1.25)	1.24 (1.02–1.50)	1.06 (0.87–1.29)	1.36 (1.09–1.70)	0.02
Pre-fortification era (1980/1986–1998)							
No. of cases	215	324	123	114	101	96	
Multivariate RR *	1.00	1.07 (0.83–1.37)	1.03 (0.82–1.30)	1.26 (0.99–1.60)	1.01 (0.78–1.29)	1.31 (1.00–1.71)	0.10
Post-fortification era (1998–2008)							
No. of cases	169	134	66	51	43	28	
Multivariate RR *	1.00	1.04 (0.82–1.32)	1.21 (0.87–1.68)	1.13 (0.56–2.30)	1.11 (0.72–1.70)	1.07 (0.69–1.65)	0.67

* Multivariate RRs are adjusted for age, gender (combined data only), total pack-years of smoking (<10, 10-<30, 30-<50, 50-<70, 70+), physical activity (quintiles of metabolic equivalent tasks/wk), body mass index (BMI) (<23, 23-<25, 25-<30, 30-<35, and 35+ kg/m^2), height (continuous), family history of colorectal cancer in parents and siblings (yes, no), history of endoscopy (yes, no), aspirin use (never, past, current use of 1–2, ≥3 tablets/wk), postmenopausal hormone (PMH) use (only in women; premenopausal, never, past, and current), red meat intake (quintiles), calcium intake from foods (continuous), and total energy intake (continuous)

** *P* for heterogeneity by fortification period was 0.44.